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REMARKS

The present application was originally filed with 18 Claims. In a Restriction Requirement mailed January 29, 2004, the Examiner restricted the Claims into two species, namely:

- a) Methods of obtaining variants using crystal structures; and
- b) Methods of obtaining variants not using crystal structures.

In a Response filed March 1, 2004, Applicants elected the species in Group a), directed towards methods of obtaining variants using crystal structures, with traverse. Applicants understood that Claims 14-18 were to be examined first, but if no prior art was found, all of the Claims were to be examined in the first Office Action.

In the present Office Action, the Examiner acknowledged Applicant's election of species (a) in the present case and indicated the Information Disclosure Statement was reviewed and entered. Applicants note that the Examiner has requested a paper copy of the Sequence Listing and a Statement of Sameness. Copies of the documents filed July 30, 2002 are provided herewith.

The Examiner has objected to the Title, as allegedly not being descriptive of the elected species. Applicants appreciate the Examiner's suggestions and have amended the Title as suggested. Applicants also note that the Examiner has objected to the Abstract. Applicants have amended the Abstract and believe that it is proper.

The Examiner has also objected to Claims 14 and 18 as allegedly having "arduous claim structure." (Office Action, page 3). The Examiner suggested using a list, such as a), b), c), etc. to define the 6 method steps of the Claims for clarity. Applicants appreciate the Examiner's suggestions and have amended the Claims to a list format, to make reading the Claims easier.

The Examiner's rejections are addressed in the following order:

- 1) Claims 14-18 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite;
- 2) Claims 14-15 and 17 stand rejected under 35 U.S.C. §101/103(a), second paragraph, as allegedly being anticipated or obvious; and
- 3) Claims 16 and 18 stand rejected under 35 U.S.C. §103(a) as allegedly being obvious.

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1) The Claims are Definite

The Examiner has rejected Claims 14-18 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. In particular, the Examiner argues that the iteration step in Claims 14 and 18 is unclear. The Examiner indicates that the concept of "repeat" site-saturation is confusing, in that saturation mutagenesis produces all possible mutations. The Examiner further questions whether 3D rendition is used repeatedly in the grading system.

In order to more clearly recite the claimed invention, Applicants have amended the Claims to recite that the site-saturation mutagenesis is performed specifically on variants identified based on their desired properties. Thus, while the site-saturation mutagenesis in step b) provides mutations at each site, the repetition of the site-saturation mutagenesis on specific variants provides additional information regarding the specific mutation(s) at the mutated sites in the variants. The subsequent rounds of mutagenesis provide variants with additional mutations at specific sites. Thus, the variant produced in the first round of site-saturation mutagenesis is used as the "parent" enzyme in subsequent rounds of site-saturation mutagenesis. Therefore, where the first variant has one mutation (in comparison with the original parent enzyme), the variants in the second generation have an additional mutation. Each subsequent round of testing produces variants with additional numbers of mutations. The choice of variants for each subsequent round of mutagenesis is based on the grading and feedback results obtained after each round of mutagenesis.

In terms of the use of the 3D rendition, it is optionally used in the method to assess the variants as they are generated and analyzed using the methods of the claimed invention (See e.g., page 8). Applicants have added new Claims 20 and 22, which recite that step a) (3-dimensional rendition generation) is performed on the variant of interest. New Claims 19 and 21 recite that the steps subsequent to step a) in Claims 14 and 18 are repeated. Support for these new Claims is found throughout the Specification as filed and no new matter is added in these new Claims. In addition, in order to more clearly recite the claimed invention, Applicant has amended Claim 18 to read "rendition."

In addition, the Examiner has rejected Claims 14-18 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite, arguing that the terms "three-dimensional rendition" and "three dimensional model" are confusing as they are used

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in two different Claims. The Examiner indicates that the three-dimensional crystal (or x-ray) structures are known for *F. solani* cutinase, and that these structures are high resolution (<2.0 angstroms). The Examiner requests clarification as to the meaning of these terms. In particular, the Examiner has inquired as to whether "rendition" or "model" refers to high-resolution structures, as "rendition" implies more "low resolution" than model. As indicated above, the Claims have been amended in order to more clearly recite the claimed invention. It is not intended that the invention be limited to any particular method, as any method that provides a three-dimensional rendition of a molecule (e.g., enzyme) of interest finds use in the presently claimed invention.

2) The Claims are Unobvious Over Poulouse and/or Short et al.

The Examiner has rejected Claims 14-15 and 17, under 35 U.S.C. §102/103(a), second paragraph, as allegedly being anticipated or obvious under Poulouse (U.S. Pat. No. 5,352,594; the "Poulouse Patent"), in view of Short (U.S. Pat. No. 6,171,820; the "Short Patent"). In particular, the Examiner argues that Poulouse teaches a method for making mutant enzymes with altered substrate activities and that a preferred enzyme is cutinase from *P. mendocina*, whose sequence is a truncated form of SEQ ID NO:1 herein. The Examiner further indicates that selection of mutation site(s) is performed by choosing residues within 15 angstroms of the active site or at positions within 6 amino acids of active site residues.

The Examiner argues that "[a]t the time of the invention, methods of producing variant enzymes using (a) site-saturation mutagenesis, as indicated by structural data, (b) screening, and (c) repeating with screened products having desirable activities was obvious because defining a particular single-site mutant as useful and using said single-site mutant for further mutagenesis producing even more useful double mutants is [sic] an efficient use of time and resources as opposed to making all possible combinations of double mutants first. One would have been motivated to practice said iteration using time- and resource-saving practices because said practices are practical laboratory techniques. One would have had a reasonable expectation of success in production of double, etc. mutants by an iterative process because the process is identical except for the template." (Office Action, pages 6-7).

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Applicants must respectfully disagree with the Examiner's arguments. With regard to anticipation, the law is clear that:

"Invalidity for anticipation requires that all of the elements and limitations of the claim are found within a single prior art reference. . . . There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention."²

There is no teaching in either Poulouse Patent nor the Short Patent of using structural data obtained from structural analyses (*i.e.*, 3-D rendition) of a parent enzyme to identify residues for site-saturation mutagenesis at these sites, mutagenizing these sites, selecting mutant variants with particular activities, grading or scoring these mutant variants with regard to these properties, then using these variants as starting material to repeat these mutagenesis methods, scoring, and analyzing additional variants. Although the Poulouse Patent teaches optimization of results of mutagenesis, there is no suggestion in this Patent of each and every step of the presently claimed invention. Thus, there is no anticipation of the Claims based on the Poulouse Patent.

Likewise, Applicants must respectfully submit that the Short Patent does not teach each and every element of the presently claimed invention. Although the Short Patent teaches saturation mutagenesis in an iterative manner, there is no teaching of grading variants and using this information to direct further mutagenesis. Again, there is no anticipation of the Claims by the Short Patent.

In regards to obviousness, Applicants contend that an obviousness rejection must rest on a factual basis, and these facts must be interpreted without hindsight reconstruction of the invention from the prior art. In making this evaluation, all of the facts must be considered, and the Examiner must supply the factual basis for the rejection. The Examiner may not, because she doubts that the invention is patentable, resort to speculation, unfounded assumptions, or hindsight reconstruction to supply deficiencies in the factual basis for the rejection. *See, In re Warner*, 379 F.2d 1011, 154 USPQ 173 (CCPA 1967). Furthermore, as stated by

² *Scripps Clinic & Research Fdn. v. Genentech, Inc.*, 927 F.2d 1565, 1576 (Fed. Cir. 1991).

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the Federal Circuit, (*W.L. Gore & Assoc. v. Garlock, Inc.*, 721 F.2d 1540, 1550, 220 USPQ 303, 311 [Fed. Cir. 1983]):

To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher.

Applicants believe that this may be the situation in the present case. Whether taken alone or in combination, the prior art references cited by the Examiner do not provide any teaching or suggestion of the claimed invention. A *prima facie* case of obviousness requires the Examiner to cite to a combination of references which (a) suggests or motivates one of skill in the art to modify their teachings to yield the claimed invention, (b) discloses the elements of the claimed invention, and (c) provides a reasonable expectation of success should the claimed invention be carried out. Failure to establish any one of these requirements precludes a finding of a *prima facie* case of obviousness and, without more, entitles Applicant to withdrawal of the rejection of the claims in issue.³ Applicants respectfully submit that neither of the references taken alone or in combination provides any suggestion or motivation to combine their teachings, nor does this combination result in the presently claimed invention, as all of the elements are not disclosed by the prior art. Indeed it is axiomatic for establishing a *prima facie* case of obviousness that "all the claim limitations must be taught or suggested by the prior art."⁴ In addition, there is no reasonable expectation of success that the combination of the Poulouse and Short Patents would result in the presently claimed invention.

Furthermore, an essential requirement for a *prima facie* case of obviousness is whether a person skilled in the art would be motivated to modify the reference to arrive at the claimed invention.⁵ In particular,

³ See, e.g., *Northern Telecom Inc. v. Datapoint Corp.*, 15 USPQ2d 1321, 1323 (Fed. Cir. 1990); *In re Dow Chemical Co.*, 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988).

⁴ MPEP § 2143.03, citing *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974).

⁵ *In re Fine*, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598-99 (Fed. Cir. 1988) and *In re Jones*, 21 USPQ2d 1941, 1943 (Fed. Cir. 1992).

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"the examiner must show *reasons* that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the *claimed invention*, would select the elements from the cited prior art references for combination in the manner claimed."⁶

As indicated above, there is no teaching in these references, taken alone or in combination that would lead one of ordinary skill in the art to practice each and every element of the claimed invention. The Examiner may not utilize hindsight to argue that the claimed invention is obvious under the prior art references. As there is no teaching in either of these references that suggests or motivates their combination, nor even all of the elements of the claimed invention, Applicants respectfully submit that the Claims are unobvious and request that this rejection be withdrawn.

3) The Claims are Unobvious Over Poulouse, Short and Abo

The Examiner has rejected Claims 16 and 18 under 35 U.S.C. §103(a), as allegedly being unpatentable over the Poulouse Patent, in view of Abo *et al.* (WO 00/34450; the "Abo Publication"), and optionally in view of the Short Patent. The Examiner argues that "it would have been obvious to practice the methods taught by Poulouse, and optionally Short, to produce better cutinases wherein better is equivalent to [being] more active against a polyester substrate and more thermostable because said mutants are expressly proposed by Abo *et al.* although produced by different means. One would have been motivated to combine the teachings of Poulouse, optionally Short, and Abo *et al.* because of the commercial value of thermostable, active cutinases as noted by Abo *et al.* (see page 1)." (Office Action, pages 7-8). While Applicants agree with the Examiner that the combination of the Poulouse Patent, optionally the Short Patent and the Abo Publication could result in commercially valuable cutinases with thermostable activity, there is no teaching in any of the cited references, taken alone or in combination, that would result in the presently claimed invention.

⁶ (Emphasis added) *In re Rouffet*, 47 USPQ2d 1453 (Fed. Cir. 1998); *Robotic Vision Systems Inc. v. View Engineering Inc.*, 51 USPQ2d 1948 (Fed. Cir. 1999).

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As discussed above, the presently claimed invention is unobvious over the Poulos Patent and the Short Patent. The addition of the Abo Publication does not remedy the deficiencies in these prior art references such that the combination of these three references produces the presently claimed invention. The Abo Publication teaches cutinases that have improved thermostability. These cutinases are produced using site-directed mutagenesis. Mutant enzymes produced by this mutagenesis step are tested for their thermostability and their activity on substrates. There is no teaching nor suggestion of each step of the presently claimed invention (e.g., iterative site-saturation mutagenesis, grading, identifying additional sites for mutagenesis, and subsequent rounds of mutagenesis. In sum, as there is no teaching of the presently claimed invention in these references, whether taken alone or in combination, Applicants respectfully submit that the present Claims are unobvious and request that this rejection be withdrawn.

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CONCLUSION

All grounds of rejection and objection of the Office Action of May 14, 2004, having been addressed, reconsideration of the application is respectfully requested. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicant encourages the Examiner to call the undersigned at (650) 846-5838.

Respectfully submitted,

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